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Multiplicative and additive interactions between risk factors for coronary heart disease

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There are a series of well-established risk factors of coronary heart disease (CHD): hypertension, high total cholesterol, smoking, diabetes, older age and male sex [1]. Some studies have paid attention to interactions between them, but have mainly looked at multiplicative interactions with age and/or sex. For example, relative risks associated with many risk factors are larger at younger compared to older ages [2]. The dominant approach to quantifying the association of risk factors with disease is the use of multiplicative models, such as Cox regression. They allow estimation of the association between risk factor and disease as a ratio in hazard between exposed and unexposed groups as well as estimation of the multiplicative interactions between risk factors. An alternative approach is to fit additive hazards model that provides the excess risk due to the presence of risk factor and opportunity to quantify interactions on additive scale [3]. The examination of interactions on the additive scale is rarely done, despite calls for the wider use of absolute measures in epidemiology and public health practice [4,5].

In this study we use data from UK Biobank (UKB) [6], 336,383 participants of 40–70 years old at baseline, who were free of CHD and stroke at baseline and did not report lipid lowering and blood pressure medication use, to identify interactions between hypertension, high total cholesterol, and smoking for risk of CHD on both in multiplicative (Cox regression) and additive (additive hazard models) scales. The outcome of interest was combined incident fatal or non-fatal CHD (ICD-10 codes I21-I25) obtained through the linkage to health records with mean follow-up time of 10 years. Due to known differences in effect estimates depending on age, we did analyses separately for 40–60 and 60–83 years keeping age as the underlying time axis for the analyses.

In the age group 40–60 years we estimated that there were 5.3 (95% CI 2.1, 8.5) more cases of CHD per 10,000 person years due to superadditive interaction between hypertension and high total cholesterol, 17.6 (95%CI 11.2, 24.0) more cases of CHD per 10,000 due to superadditive interaction of hypertension and smoking, and 12.3 (95%CI 7.6, 17.0) more cases of CHD per 10,000 due to superadditive interaction of smoking and high cholesterol (Table 1). At ages 60–80 years there was evidence of supermultiplicative interaction for hypertension and total cholesterol, HR (Hazard Ratio) 1.17 (95% CI 1.02,1.34) and submultiplicative interaction for hypertension and smoking, HR 0.77 (95% CI 0.67, 0.87) (Table 1).

This is the first systematic attempt to assess whether there is the deviation from multiplicativity of CHD risk factors in Cox models and deviation from additivity in additive hazards model. The results reveal that at ages 40–60 years, there is evidence of interaction between main risk factors (hypertension, high cholesterol, smoking) on the additive but not on the multiplicative scale. At ages 60–83 years there is evidence of interaction on the multiplicative scale but not on the additive, demonstrating that interaction should be assessed both relatively and additively. In short, we observed different interaction patterns depending on age. Thus, examining both additive and multiplicative interactions should be considered for CHD given their implications for explaining the differences in CHD between subgroups and planning of public health policies.

Identifying the deviation from risk additivity in prediction of CHD in younger age groups (40–60 years), we demonstrated that persons with one risk factor were shown to be more vulnerable to the effects of second risk factor on CHD risk ("differential vulnerability"). Epidemiological research has attempted to explain the relative social gradient in CHD by assuming that different prevalence of conventional CHD risk factors in socioeconomic strata would mediate the association between socioeconomic position and CVD. Analysis on the relative scale which is done either by adjustment for conventional risk factors in the multiplicative models or in mediation analysis explained only a modest proportion of the relative social inequality in CHD [7]. Such results were first interpreted to mean that most of the effects of social inequality on CHD do not work through mechanisms linked to conventional risk factors, and so

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Table 1
Interactions between hypertension, high total cholesterol, and current smoking to predict CHD estimated using Cox proportional hazards regression and the additive hazards regression based in UK biobank, N = 219,561 (40–60 years old) and N = 240,463 (60–83 years old), without history of CHD at baseline and not using blood pressure or lipid lowering drugs.

	AGE at risk 40–59 years		AGE at risk 60–83 years	
	Number of events - 2672		Number of events – 7091	
	Cox Proportional Hazards Model Hazard Ratio (95% CI)*	Additive Hazard Model No. Additional Coronary heart disease cases per 10,000 Person Years (95% CI)*	Cox Proportional Hazards Model Hazard Ratio (95% CI)*	Additive Hazard Model No. Additional Coronary heart disease cases per 10,000 Person Years (95% CI)*
1) ***Model including interaction between blood pressure and total cholesterol; controlling for sex, smoking, diabetes***				
Hypertensive vs. Normotensive among those with optimal cholesterol	2.21 (1.81,2.71)	7.2 (4.6, 9.9)	1.32 (1.17,1.49)	10.55 (5.4, 15.6)
High total cholesterol vs. optimal total cholesterol in those who were normotensive	1.95 (1.68,2.26)	5.5 (4.4, 6.6)	1.03 (0.93,1.14)	2.33 (−0.8, 5.5)
Interaction of hypertension with high total cholesterol	0.82 (0.66,1.02)	5.3 (2.1, 8.5)	1.17 (1.02,1.34)	5.23 (−0.2, 10.7)
Test for interaction (P-value)	0.073	< 0.001	0.021	0.06
2) ***Model including interaction between hypertension and smoking; controlling for sex, high total cholesterol, diabetes***				
Hypertensive vs. normotensive in non-smokers	1.91 (1.75,2.09)	9.2 (7.7, 10.6)	1.58 (1.49,1.66)	14.9 (13.1, 16.7)
Current smoker vs. non-smoker in those who were normotensive	2.53 (2.25,2.86)	14.0 (11.5, 16.5)	2.12 (1.93,2.34)	29.5 (24.4, 34.6)
Interaction of hypertension and smoking	0.92 (0.77,1.09)	17.6 (11.2, 24.0)	0.77 (0.67,0.87)	2.6 (−5.8, 11.1)
Test for interaction (P-value)	0.312	< 0.001	< 0.001	0.540
3) ***Model including interaction between high total cholesterol and smoking; controlling for sex, hypertension, diabetes***				
High total cholesterol vs optimal total cholesterol in non-smokers	1.78 (1.57,2.02)	5.3 (4.2, 6.4)	1.13 (1.05,1.21)	4.8 (2.2, 7.5)
Current smoker vs. non-smoker in those with optimal total cholesterol	2.37 (1.89,2.98)	9.9 (6.3, 13.5)	1.84 (1.57,2.17)	32.4 (21.4, 43.4)
Interaction of high total cholesterol with smoking	1.02 (0.8,1.31)	12.3 (7.6, 17.0)	0.99 (0.83,1.18)	-2.0 (−13.9, 9.9)
Test for interaction (P-value)	0.544	< 0.001	0.88	0.742

other potential causes of relative social inequalities need to be investigated. However, Lynch et al had suggested that this situation arises because of the epidemiological preference for contrasting and explaining risk on a relative rather than absolute scale [7]. Difference in absolute effect of an exposure to risk factor by another risk factor shown in our analysis supports the latter explanation. In the younger group, based on results of the multiplicative Cox model, one may conclude that there is no good evidence that the relative risks due to presence of a second risk factor are different among those who already have one risk factor (ie. high total cholesterol in hypertensives, smoking in hypertensives). Additive hazards model leads to a different conclusion by providing the estimate of incidence rates with corresponding confidence intervals for subgroups with both risk factors present. This is important from the perspective of health planning and policy which should continue to focus on reducing conventional risk factors for CHD. While some unconventional risk factors may contribute to some extent to the differences in CHD rates, they are still very likely to operate through the main known risk factors: hypertension, high blood cholesterol, smoking, diabetes. In countries with the high baseline rate of CHD, this potentially could translate into much higher numbers of additional cases of CHD, for example, in people with hypertension who also have high cholesterol and/or smoke.

Future research on interactions between CHD risk factors should be focused on quantifying the risk of CHD in participants with different combinations of risk factors accounting for interactions between them. Application of additive hazard models for CHD should be considered when selecting the populations for intervention and planning prevention measures. Additionally, the implications of these broader sets of interactions need to be accounted for when developing new clinical risk score algorithms which tend to be based on multiplicative models.

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Data access

application for the UK biobank resource, code available from corresponding author upon request.

CRediT authorship contribution statement

Olena Iakunchykova: Conceptualization, Formal analysis, Writing – original draft preparation. **Theis Lange**: Methodology, Writing – review & editing. **David Leon**: Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.annepidem.2023.11.012.

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